Intravenous immunoglobulin-resistant Kawasaki disease: Risk factors in children in a middle-income country

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ABSTRACT

Background : **Identifying risk factors in patients with intravenous immunoglobulin (IVIG) resistance Kawasaki disease (KD) is vital in managing and preventing coronary artery aneurysms (CAAs). We aimed to study the risk factors for IVIG resistance KD in Malaysian children.**

Methods : **This retrospective observational study of children with KD was conducted at two tertiary hospitals in Malaysia from January 2014 to December 2019. Multivariable binary logistic regression was used to analyze the risk factors associated with IVIG resistance.**

Results : **A total of 174 patients, 118 males (67.8%) with a median age of 1.4-year-old (interquartile range: 0.1–12.1-year-old), were analyzed. Early (<5 days) and late (>10 days) IVIG treatments were observed in 14 (8.1%) and 19 (11.0%), respectively. Thirty-two patients (18.4%) had IVIG resistance. The independent factors associated with IVIG resistance were high white cell count, hypoalbuminemia, and extremities changes with an odd ratio of 4.7, 3.0, and 4.0, respectively. In addition, CAA was significantly higher in IVIG resistance compared to IVIG responder patients (57.5% [19/33] vs. 23.4% [33/141], $P < 0.001$). The sensitivity was high in Harada (93.8%) but low in Kobayashi and Egami (46.9% and 34.4%, respectively). The specificity was high with Egami (79.6%) but low in Harada and Kobayashi (22.5% and 64.1%, respectively).**

Conclusion : **Leukocytosis, hypoalbuminemia, and extremities changes were independent risk factors for IVIG resistance. The variation in sensitivity and specificity of the Japanese scoring makes it unsuitable for predicting IVIG resistance in Malaysian children.**

Keywords : Coronary artery aneurysm, intravenous immunoglobulin resistant, Kawasaki disease, risk factor

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INTRODUCTION

Kawasaki disease (KD) is an acute medium-sized vasculitis of unknown etiology with a predilection to the coronary artery.[1,2] KD prevalence is high in the northeast Asian country, with an incidence of up to 308/100,000 in children under five.[3] The diagnosis of KD is based on clinical diagnostic criteria, and in patients with incomplete criteria, coronary aneurysms, and dilation from two-dimensional (2D) echocardiography aid in the diagnosis.[4,5]

Timely treatment with intravenous immunoglobulin (IVIG) has reduced the prevalence of coronary artery aneurysm (CAA) significantly.[6] However, about 10%–20% of patients with KD had persistent and recurrent fever after the completion of initial IVIG, with a higher risk in males, early IVIG treatment, high inflammatory marker, or liver dysfunction.[6-10] In addition, children with IVIG resistance are at a higher risk for developing CAAs. In untreated patients, CAAs developed in one in four KD.[11]

Several risk scores in Japanese children have been developed to predict IVIG resistance.[12-14] Japanese scoring systems such as Harada,[15] Kobayashi,[16] and Egami[17] have been validated in many countries with various reported sensitivity and specificity.[18-20] However, these scores have not been validated among children in Malaysia or other south Asian countries. Due to the multiethnicity in Malaysia, we hypothesize that these scores may not have a good sensitivity and specificity in predicting IVIG resistance among Malaysian children.

Therefore, this study aims to study the risk factors for IVIG-resistant KD in Malaysian children through clinical manifestations and laboratory parameters.

METHODS

This retrospective observational study of children with KD at Hospital Tunku Azizah Kuala Lumpur (HTAKL) and University Malaya Medical Centre (UMMC) was conducted between January 1, 2014, and December 31, 2019. HTAKL and UMMC are the tertiary referral center for KD in Klang Valley. Klang Valley is home to 8.42 million population with six public and thirty private hospitals. In addition, HTAKL and UMMC received referrals from the public and private hospitals in Klang Valley and refractory KD patients from other states in Malaysia.

Data collection

The demographic, clinical, laboratory, and 2D echocardiography data were retrieved from the medical record from each center. Ethics approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia (National Medical Research Register 18-3981-44812), and UMMC Ethics Board (ID 2020116-8186). Patients with incomplete data and without IVIG treatment were excluded from the study.

Definition

KD was diagnosed based on recent guidelines by McCrindle *et al.*[6] Briefly, a patient is considered to have a complete KD if they have at least four and incomplete KD if patients have less than four diagnostic criteria. CAA was defined based on Z-score (Z-score >2.5) described by Dallaire & Dahdah and was calculated using the Z-score calculator.[21] The CAA was further divided into small, medium, and giant aneurysms. IVIG resistance is defined as persistent or recrudescent fever at least 36 h after the completion of the first IVIG infusion.[22]

2D echocardiography was performed at the time of diagnosis and reviewed by a pediatric cardiologist at each center. All patients had a 2D echocardiogram approximately 6–8 weeks after diagnosis and were followed up regularly at 6–12 monthly intervals.

The risk score for each patient was calculated using Harada, Kobayashi, and Egami scoring systems during the study. The proportion of high-risk patients was compared for each risk score. The Sano scoring system is not used due to incomplete serum bilirubin data in most patients.

The treatment for KD is based on the clinical practice guideline in Malaysian pediatric protocol.[23] All confirmed KD will receive a single infusion of 2 g/kg of immunoglobulin over 10–12 h. The second infusion of IVIG or intravenous methylprednisolone is used for IVIG-resistant patients.

After completion of IVIG, patients received an anti-inflammatory aspirin dose of 30–50 mg/kg/day divided in 3–4 doses. Once the fever subsides for 48 h, aspirin will be reduced to 5 mg/kg/dose daily. The aspirin will be discontinued once the inflammatory markers and platelet count have normalized and echocardiography showed normal or resolved coronary artery dilation during subsequent follow-up.

Statistical analysis

All data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation or median (interquartile range [IQR]). Categorical variables were presented as counts with percentages. Fisher's exact test was used to compare categorical data. Student's *t*-test was used to compare continuous data groups. Sensitivity and specificity for each scoring system were calculated. Receiver operating characteristic (ROC) curves were

plotted for each prediction analysis and specificity of each scoring system. Multivariable binary logistic regression analysis was performed to identify the independent risk factors for IVIG resistance. P <0.05 was considered statistically significant.

RESULTS

There were 200 KD patients from both centers during the study. However, 26 patients were excluded (21 incomplete data and five did not receive IVIG). The median age of 174 KD patients included in the study was 1.4 years old, ranging from 1 month to 12.1 years old. The male-to-female ratio was 2.1:1, and 133 (76.4%) complete and 41 (23.6%) incomplete KD patients. The median IVIG treatment was at 7 days (IQR: 6, 8 days), with 19 (11.0%) given after 10 days of illness [Table 1].

Of the 174 patients, 142 (81.6%) were IVIG responders, and 32 (18.4%) were IVIG resistant. Of the 32 patients with IVIG resistance, 19 received a second dose of IVIG only, ten combinations of IVIG with steroids, and three received steroids only. All except two patients responded to the treatment given. IVIG-resistant patients are younger and have a high proportion of extremities changes, higher levels of white cell count, lower hemoglobin, hematocrit, and serum albumin compared to the IVIG responder group [Table 1].

Logistic regression analysis for intravenous immunoglobulin resistance risk factors

Univariate analysis revealed that extremities changes, white blood cell (WBC) of more than 15 × 10^9/L, hematocrit <30%, and albumin <32 g/l were significantly associated with IVIG resistance. However, after adjusting for age, sex, and ethnicity, only the presence of extremities changes, WBC more than 15 × 10^9/L, and albumin <32 g/l were independent factors associated with IVIG resistance [Table 2].

Coronary artery aneurysm and intravenous immunoglobulin resistant

Forty-four patients (25.3%) developed CAA (29 small, 13 medium, and two giant aneurysms). There is a statistically significant difference in IVIG-resistant patients with CAA compared to IVIG responder patients (57.5% [19/33] vs. 23.4% [33/141], P < 0.001).

Comparison between Harada, Kobayashi, and Egami scoring systems

Among the three scoring systems, Harada showed significant differences between the IVIG responder and

Table 1: Comparison of patients with intravenous immunoglobulin responder and nonresponder

Variables	All (*n*=174), *n* (%)	IVIG responder (*n*=142), *n* (%)	IVIG resistance (*n*=32), *n* (%)	*P**
Age (years), median (IQR)	1.4 (0.1-12.1)	1.5 (0.8-2.9)	0.9 (0.5-1.9)	0.08
Gender				
Male	118 (67.8)	97 (68.8)	21 (63.6)	0.77
Female	56 (32.2)	45 (31.7)	11 (34.4)	
Ethnic				0.19
Chinese	49 (28.2)	37 (26.2)	12 (37.5)	
Nonchinese	125 (71.8)	105 (73.9)	20 (62.5)	
KD type				0.10
Complete	133 (76.4)	105 (73.9)	28 (87.5)	
Incomplete	41 (23.6)	37 (26.1)	4 (12.5)	
Presenting symptoms				
Rash	153 (87.9)	123 (86.6)	30 (93.8)	0.26
Cervical lymphadenopathy	131 (75.3)	105 (73.9)	26 (81.3)	0.39
Conjunctivitis	141 (81.0)	117 (82.4)	24 (75.0)	0.33
Extremities changes	121 (69.5)	93 (65.5)	28 (87.5)	0.02
Oral mucosa changes	133 (76.4)	105 (73.9)	28 (87.5)	0.10
BCG scar flaring	63 (36.2)	48 (33.8)	15 (46.9)	0.16
Perianal excoriation	32 (18.5)	28 (19.9)	4 (12.5)	0.33
Early IVIG (<5 days)				
Yes	14 (8.0)	9 (6.3)	5 (15.6)	0.08
No	160 (92.0)	133 (93.7)	27 (84.4)	
Hemoglobin (g/L), mean±SD	10.4±1.4	10.5±1.6	9.8±1.5	0.02
Hematocrit (%), mean±SD	31.0±4.6	31.6 (29.4-33.9)	29.1 (24.1-33.2)	0.005
White cell count (×10^9/L), mean±SD	17.8±7.6	15.1 (11.9-20.6)	19.6 (17.5-27.5)	<0.001
Neutrophils (%), mean±SD	59.3±19.0	58.8±19.3	61.1±17.9	0.21
Platelet (×10^9/L), mean±SD	421±208	393 (311-522)	366 (245-433)	0.06
CRP (mg/L), median (IQR)	12.1 (6.4-20.9)	10.8 (5.1-20.4)	14.8 (8.8-22.0)	0.11
ESR (mm/h), median (IQR)	64.5 (48.0-100.0)	64 (48-100)	67 (48-101)	0.85
Albumin (g/L), mean±SD	33.3±6.0	33.9±5.7	30.7±6.5	0.01
Sodium (mmoL/L), mean (IQR)	135 (133-137)	135 (133-137)	135 (132-136)	0.12
AST (IU/L), median (IQR)	32 (23-52)	32 (22-50)	33 (24-62)	0.50
ALT (IU/L), median (IQR)	35 (20-89)	35 (20-83)	44 (17-92)	0.81

*P<0.05 is significant. CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, IQR: Interquartile range, IVIG: Intravenous immunoglobulin, BCG: Bacillus Calmette-Guérin

Table 2: Associated risk factors for intravenous immunoglobulin resistance among Malaysian children with Kawasaki disease

Variables	Total	IVIG resistance, *n* (%)	Crude OR (95% CI)	*P*	AOR (95% CI)[a]	*P*
Age <1 (year)						
Yes	63	16 (25.4)	1.53 (0.70-3.31)	0.28	1.04 (0.41-2.62)	0.94
No	111	16 (14.4)	1.00 (reference)		1.00 (reference)	
Sex						
Female	56	11 (19.6)	0.88 (0.39-1.99)	0.77	1.47 (0.57-3.79)	0.21
Male	118	21 (17.8)	1.00 (reference)		1.00 (reference)	
Ethnicity						
Chinese	49	12 (24.5)	1.70 (0.76-3.82)	0.19	2.14 (0.86-5.32)	0.10
Non-Chinese	125	20 (16.0)	1.00 (reference)			
Extremities changes						
Yes	121	28 (23.1)	2.30 (1.05-5.02)	0.04	4.03 (1.24-13.12)	0.02
No	53	4 (7.5)	1.00 (reference)		1.00 (reference)	
WBC>15x10^9/L						
Yes	101	27 (26.7)	4.96 (1.81-13.62)	0.002	4.72 (1.59-13.99)	0.005
No	73	5 (6.8)	1.00 (reference)		1.00 (reference)	
Hematocrit <30%						
Yes	55	16 (29.1)	2.64 (1.20-5.78)	0.01	2.27 (0.86-5.98)	0.09
No	119	16 (13.4)	1.00 (reference)		1.00 (reference)	
Albumin <32 g/L						
Yes	59	18 (30.5)	3.14 (1.43-6.89)	0.004	3.01 (1.18-7.64)	0.02
No	114	14 (12.3)	1.00 (reference)		1.00 (reference)	

[a]Analyzed with multivariable binary logistic regression, enter method, corrected for age, sex, and ethnic group. OR are considered statistically significantly different from the reference category if their 95% CIs exclude one. CI: Confidence interval, OR: Odds ratios, AOR: Adjusted OR, IVIG: Intravenous immunoglobulin, WBC: White blood cell

Table 3: Comparison of intravenous immunoglobulin resistance and responder using Harada, Kobayashi, and Egami scoring systems

Scoring system	Positive and negative score	IVIG resistant, *n* (%)	IVIG responder, *n* (%)	*P*
Harada	Positive score (high risk)	30 (21.4)	110 (78.6)	0.036
	Negative score (low risk)	2 (5.9)	32 (94.1)	
Kobayashi	Positive score (high risk)	15 (22.7)	51 (77.3)	0.248
	Negative score (low risk)	17 (15.7)	91 (84.3)	
Egami	Positive score (high risk)	11 (27.5)	29 (72.5)	0.090
	Negative score	21 (15.7)	113 (84.3)	

P<0.05 is significant. IVIG: Intravenous immunoglobulin

IVIG-resistant groups [Table 3]. Specific analysis for each ethnicity found a significant difference in Harada score variables in Malay patients, $P = 0.025$. Harada score is more sensitive in Malay patients at 95.8% compared to Chinese patients at 76.5%. However, the specificity is almost the same at 25%. For other risk scores, the Kobayashi score has higher sensitivity at 41.7% for the Malay compared to Chinese patients at 26.4%. For Egami, Malay patient has a lower sensitivity at 16.7% compared to Chinese patient at 29.4%.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each risk score system are shown in Table 4. The sensitivity of each scoring system was high in Harada but low in Kobayashi and Egami (93.8%, 46.9%, and 34.4%, respectively), and the specificity was low in Harada and highest in Egami (22.5%, 64.1%, and 79.6%, respectively). For the ROC curve area comparison, there is a minimal difference between the scores.

DISCUSSION

IVIG resistance is a significant factor associated with CAAs.[24,25] Thus, identifying the risk factors associated with IVIG resistance allows the early use of additional therapies to avoid the development of coronary aneurysms. In this study, we evaluate the risk factors for IVIG resistant in children with KD.

IVIG resistance rate in this cohort was high at 20% compared to other population-based study from Malaysia, with a rate of 7.4%.[26] Nevertheless, it is still within the recent meta-analysis studies, ranging from 5% to 35%.[9,11] The higher rate of IVIG resistance in this study could be due to the study population, which involved two major referral centers in Klang Valley, Kuala Lumpur.

Our study found that WBC of more than 15×10^9/l, albumin <32 g/l, and the presence of extremities changes were associated factors for IVIG resistance. This result correlates with a recent meta-analysis by Liu *et al.*[9] In identified resistant cases, infliximab could be the choice rather than IVIG to prevent aneurysms or mitigate the severity of coronary artery disease. However, as only three predictors were found in this study, a new risk score for predicting IVIG resistance in this cohort could not be developed. More extensive clinical, demographic, and laboratory data are needed to develop new KD risk scores for the Malaysian population.

The sensitivity and specificity vary among the three Japanese scoring systems when used in Malaysian children. A good sensitivity was noted with Harada only and poor with Egami and Kobayashi scoring system.

Table 4: The sensitivity, specificity, positive predictive value, and negative predictive value for each risk score system

Scoring system	95% CI				
	Sensitivity	Specificity	PPV	NPV	Accuracy
Harada	93.8 (79.9-99.2)	22.5 (15.9-30.3)	21.4 (19.3-23.6)	94.1 (80.1-98.4)	35.6 (28.5-43.2)
Kobayashi	46.9 (29.0-65.2)	64.1 (55.6-71.9)	22.7 (16.0-31.1)	84.3 (79.1-88.3)	60.9 (53.2-68.2)
Egami	34.4 (18.5-53.2)	79.6 (72.0-85.8)	27.5 (17.5-40.3)	84.3 (80.5-87.5)	71.2 (63.9-77.8)

CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

Meanwhile, the specificity was good with Egami and poor with other scoring systems. All three-scoring systems have a low PPV of <28% but a high NPV of >75%. These results correlate with published studies from different countries that reported variable results on the diagnostic performance of these scores in predicting IVIG resistance.[21,27-29] In China, Fu *et al.*[30] compared Kobayashi and Egami scores with their new scoring system. Their new scoring system showed better performance with 54% sensitivity, 71% specificity, and an area under the curve of 0.72. The new score includes polymorphous exanthema, perianal skin, days of illness at initial treatment, percentage of neutrophils, C-reactive protein, serum albumin, and total bilirubin.

A combination of two or three scoring systems may help to identify resistance cases. This is because scoring points and items are different and using one scoring system may not work. Harada and Egami combination may be considered in our patients as both showed high sensitivity and specificity, respectively.

These findings may be explained by the different variables used in the three scoring systems. The high prevalence of anemia of 18%–30% in children in Malaysia[31,32] may contribute to the point in the Harada scoring system and explain the differences in the validity between the three scoring systems. Even though hematocrit was the parameter used for Harada, hemoglobin is interrelated with hematocrit. The presence of anemia even before the diagnosis of KD could be one factor that may explain our findings. Other possibilities are due to multiracial and genetic variation. A published study showed that anemia is directly related to the significant upregulation of hepcidin expression in KD patients.[33] The changes in hepcidin levels following treatment with IVIG were found to be related to IVIG resistance and CAA formation.[34]

Limitations

The limitation of this study is the small number of patients with IVIG resistance. Even though the power of the sample is adequate, the sample size is relatively small compared to other studies. In addition, we have missing data due to this study being a retrospective study. The variable ethnic groups with unequal numbers of patients in each ethnic group will also affect the analysis.

CONCLUSION

The current Japanese scoring system for predicting IVIG resistance may be unsuitable for Malaysian children due to variations in the sensitivity and specificity of the scoring systems. However, combinations of scoring systems may be helpful in identifying resistant cases. IVIG resistance was correlated with high WBC, hypoalbuminemia, and extremities changes noted in KD Malaysian population. Hence, we recommend incorporating other centers in Malaysia to formulate a new scoring system for predicting IVIG-resistant cases in Malaysian KD cases which could be useful for early treatment.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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